

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: NDA 9330/S020

APPROVAL LETTER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 9-330/S-020
NDA 18-118/S-016

JUL 15 1998

Glaxo Wellcome, Inc.
Attention: Ms. Elizabeth A. Nies
Five Moore Drive
Research Triangle Park, NC 27709

Dear Ms. Nies:

Please refer to your May 12, 1998 supplemental new drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lanoxin (digoxin) Injection and Pediatric Injection (NDA 9-330) and Lanoxicaps (digoxin in solution) Capsules (NDA 18-118).

We acknowledge receipt of your submission dated June 9, 1998 to each application.

These supplemental new drug applications provide for final printed labeling revised to be consistent with the recently approved package insert for Lanoxin Tablets (NDA 20-405).

We have completed the review of these supplemental applications, as amended, and have concluded that adequate information has been presented to demonstrate that the drug products are safe and effective for use as recommended in the final printed labeling included in your June 9, 1998 submission. Accordingly, these supplemental applications are approved effective on the date of this letter.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

At your next printing, please make the following revisions:

Under **CLINICAL PHARMACOLOGY, Chronic Heart Failure**, third paragraph, first line, please change
to "... with a trend to increase time ..."

We also recommend that the storage statement under **HOW SUPPLIED** be revised as follows:

A supplemental application need not be submitted to implement either of these changes; they should, however, be reported in your next annual report.

NDA 9-330/S-020
NDA 18-118/S-016
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If you have any questions, please contact:

Mr. Gary Buehler
Regulatory Health Project Manager
(301) 594-5332

Sincerely yours,

7/15/98

Raymond J. Lipicky, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:

Archival NDAs 9-330/, 18-118
HFD-110/Div. Files
HF-2/MedWatch (with labeling)
HFD-002/ORM (with labeling)
HFD-101/ADRA (with labeling)
HFD-40/DDMAC (with labeling)
HFD-613/OGD (with labeling)
HFD-95/DDMS (with labeling)
HFD-810/DNDC Division Director
DISTRICT OFFICE
HFD-110/G.Buehler/7/2/98;7/13/98
sb/7/6/98;7/14/98
Initialed by: D Cunningham/7/13/98
K Srinivasachar/7/13/98
N Morgenstern/7/13/98

filename: n9330s020n18118s16ap.doc

Approval Dates: 9330 – 9/6/91
18118 – 7/26/82

7/15/98

APPROVAL (AP)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 9330/S020

FINAL PRINTED LABELING

FINAL PRINTED LABELING

LANOXIN® (digoxin) Injection Pediatric
Package InsertLabeling: originalNDA No: 9-330 No'd. 6-10-98Reviewed by: Buehler 7/2/98

APPROVED

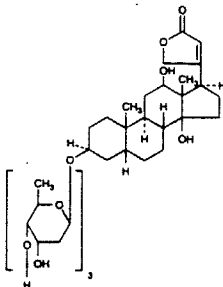
JUL 15 1998

PRODUCT INFORMATION

LANOXIN® (digoxin) Injection Pediatric
100 mcg (0.1 mg) in 1 mL

DESCRIPTION: LANOXIN (digoxin) is one of the cardiac (or digitalis) glycosides, a closely related group of drugs having in common specific effects on the myocardium. These drugs are found in a number of plants. Digoxin is extracted from the leaves of *Digitalis lanata*. The term "digitalis" is used to designate the whole group of glycosides. The glycosides are composed of two portions: a sugar and a cardenolide (hence "glycosides").

Digoxin is described chemically as (3 β ,5 β ,12 β)-3-[(2,6-dideoxy- β -D-ribo-hexopyranosyl-(1 \rightarrow 4)-O-2,6-dideoxy- β -D-ribo-hexopyranosyl-(1 \rightarrow 4))-2,6-dideoxy- β -D-ribo-hexopyranosyl]oxy]-12,14-dihydroxy-card-20(22)-enolide. Its molecular formula is C₄₁H₆₄O₁₄, its molecular weight is 780.95, and its structural formula is:



Digoxin exists as odorless white crystals that melt with decomposition above 230°C. The drug is practically insoluble in water and in ether, slightly soluble in diluted (50%) alcohol and in chloroform; and freely soluble in pyridine.

LANOXIN Injection Pediatric is a sterile solution of digoxin for intravenous injection. The vehicle contains 40% propylene glycol and 10% alcohol. The injection is buffered to a pH of 6.8 to 7.2 with 0.17% sodium phosphate and 0.08% anhydrous citric acid. Each 1-mL ampul contains 100 mcg (0.1 mg) digoxin. Dilution is not required.

CLINICAL PHARMACOLOGY: Mechanism of Action: Digoxin inhibits sodium-potassium ATPase, an enzyme that regulates the quantity of sodium and potassium inside cells. Inhibition of the enzyme leads to an increase in the intracellular concentration of sodium and thus (by stimulation of sodium-calcium exchange) an increase in the intracellular concentration of calcium. The beneficial effects of digoxin result from direct actions on cardiac muscle, as well as indirect actions on the cardiovascular system mediated by effects on the autonomic nervous system. The autonomic effects include: (1) a vagomimetic action, which is responsible for the effects of digoxin on the sinoatrial and atrioventricular (AV) nodes; and (2) baroreceptor sensitization, which results in increased afferent inhibitory activity and reduced activity of the sympathetic nervous system and renin-angiotensin system for any given increment in mean arterial pressure. The pharmacologic consequences of these direct and indirect effects are: (1) an increase in the force and velocity of myocardial systolic contraction (positive inotropic action); (2) a decrease in the degree of activation of the sympathetic nervous system and renin-angiotensin system (neurohormonal deactivating effect); and (3) slowing of the heart rate and decreased conduction velocity through the AV node (vagomimetic effect). The effects of digoxin in heart failure are mediated by its positive inotropic and neurohormonal deactivating effects, whereas the effects of the drug in atrial arrhythmias are related to its vagomimetic actions. In high doses, digoxin increases sympathetic outflow from the central nervous system (CNS). This increase in sympathetic activity may be an important factor in digitalis toxicity.

Pharmacokinetics: Note: The following data are from studies performed in adults, unless otherwise stated. **Absorption:** Comparisons of the systemic availability and equivalent doses for preparations of digoxin are shown in Table 1:

Table 1: Comparisons of the Systemic Availability and Equivalent Doses for Preparations of LANOXIN

Product	Absolute Bioavailability	Equivalent Doses (mcg)* Among Dosage Forms			
LANOXIN Tablets	60 - 80%	62.5	125	250	500
LANOXIN Elixir Pediatric	70 - 85%	62.5	125	250	500
LANOXICAPS®	90 - 100%	50	100	200	400
LANOXIN Injection/IV	100%	50	100	200	400

reduction in the risk of a patient having at least one hospitalization for heart failure, and a 6.5% reduction in total hospitalizations (for any cause).

Use of LANOXIN was associated with a trend in reduction in time to all-cause death or hospitalization. The trend was evident in subgroups of patients with mild heart failure as well as more severe disease, as shown in Table 3. Although the effect on all-cause death or hospitalization was not statistically significant, much of the apparent benefit derived from effects on mortality and hospitalization attributed to heart failure.

Table 3: Subgroup Analyses of Mortality and Hospitalization During the First Two Years Following Randomization

	n	Risk of All-Cause Mortality or All-Cause Hospitalization*			Risk of HF-Related Mortality or HF-Related Hospitalization*		
		Placebo	LANOXIN	Relative risk†	Placebo	LANOXIN	Relative risk†
All patients (EF \leq 0.45)	6801	604	593	0.94 (0.88-1.00)	294	217	0.69 (0.63-0.76)
NYHA I/II	4571	549	541	0.96 (0.89-1.04)	242	178	0.70 (0.62-0.80)
EF 0.25-0.45	4543	568	571	0.99 (0.91-1.07)	244	190	0.74 (0.66-0.84)
CTR \leq 0.55	4455	561	563	0.98 (0.91-1.06)	239	180	0.71 (0.63-0.81)
NYHA III/IV	2224	719	696	0.88 (0.80-0.97)	402	295	0.65 (0.57-0.75)
EF $<$ 0.25	2258	677	637	0.84 (0.76-0.93)	394	270	0.61 (0.53-0.71)
CTR $>$ 0.55	2346	687	650	0.85 (0.77-0.94)	398	287	0.65 (0.57-0.75)
EF $>$ 0.45‡	987	571	585	1.04 (0.88-1.23)	179	136	0.72 (0.53-0.99)

* Number of patients with an event during the first 2 years per 1000 randomized patients.

† Relative risk (95% confidence interval).

‡ DIG Ancillary Study.

In situations where there is no statistically significant benefit of treatment evident from a trial's primary endpoint, results pertaining to a secondary endpoint should be interpreted cautiously.

Chronic Atrial Fibrillation: In adult patients with chronic atrial fibrillation, digoxin slows rapid ventricular response rate in a linear dose-response fashion from 0.25 to 0.75 mg/day. Digoxin should not be used for the treatment of multifocal atrial tachycardia.

INDICATIONS AND USAGE:

Heart Failure: LANOXIN is indicated for the treatment of mild to moderate heart failure. LANOXIN increases left ventricular ejection fraction and improves heart failure symptoms as evidenced by exercise capacity and heart failure-related hospitalizations and emergency care, while having no effect on mortality. Where possible, LANOXIN should be used with a diuretic and an angiotensin-converting enzyme inhibitor, but an optimal order for starting these three drugs cannot be specified.

Atrial Fibrillation: LANOXIN is indicated for the control of ventricular response rate in patients with chronic atrial fibrillation.

CONTRAINDICATIONS: Digitalis glycosides are contraindicated in patients with ventricular fibrillation or in patients with a known hypersensitivity to digoxin. A hypersensitivity reaction to other digitalis preparations usually constitutes a contraindication to digoxin.

WARNINGS:

Sinus Node Disease and AV Block: Because digoxin slows sinoatrial and AV conduction, the drug commonly prolongs the PR interval. The drug may cause severe sinus bradycardia or sinoatrial block in patients with pre-existing sinus node disease and may cause advanced or complete heart block in patients with pre-existing incomplete AV block. In such patients consideration should be given to the insertion of a pacemaker before treatment with digoxin.

Accessory AV Pathway (Wolff-Parkinson-White Syndrome): After intravenous digoxin therapy, some patients with paroxysmal atrial fibrillation or flutter and a coexisting accessory AV pathway have developed increased antegrade conduction across the accessory pathway bypassing the AV node, leading to a very rapid ventricular response or ventricular fibrillation. Unless conduction down the accessory pathway has been blocked (either pharmacologically or by surgery), digoxin should not be used in such patients. The treatment of paroxysmal supraventricular tachycardia in such patients is usually direct-current cardioversion. **Use in Patients with Preserved Left Ventricular Systolic Function:** Patients with certain disorders involving heart failure associated with preserved left ventricular ejection fraction may be particularly susceptible to toxicity of the drug. Such disorders include restrictive cardiomyopathy, constrictive pericarditis, amyloid heart disease, and acute cor pulmonale. Patients with idiopathic hypertrophic subaortic stenosis may have worsening of the outflow obstruction due to the inotropic effects of digoxin.

*For example, 125 mcg LANOXIN Tablets equivalent to 125 mcg LANOXIN Elixir Pediatric equivalent to 100 mcg LANOXICAPS equivalent to 100 mcg LANOXIN Injection/IV.

Distribution: Following drug administration, a 6- to 8-hour tissue distribution phase is observed. This is followed by a much more gradual decline in the serum concentration of the drug, which is dependent on the elimination of digoxin from the body. The peak height and slope of the early portion (absorption/distribution phases) of the serum concentration-time curve are dependent upon the route of administration and the absorption characteristics of the formulation. Clinical evidence indicates that the early high serum concentrations do not reflect the concentration of digoxin at its site of action, but that with chronic use, the steady-state post-distribution serum concentrations are in equilibrium with tissue concentrations and correlate with pharmacologic effects. In individual patients, these post-distribution serum concentrations may be useful in evaluating therapeutic and toxic effects (see DOSAGE AND ADMINISTRATION: Serum Digoxin Concentrations).

Digoxin is concentrated in tissues and therefore has a large apparent volume of distribution. Digoxin crosses both the blood-brain barrier and the placenta. At delivery, the serum digoxin concentration in the newborn is similar to the serum concentration in the mother. Approximately 25% of digoxin in the plasma is bound to protein. Serum digoxin concentrations are not significantly altered by large changes in fat tissue weight, so that its distribution space correlates best with lean (i.e., ideal) body weight, not total body weight.

Metabolism: Only a small percentage (16%) of a dose of digoxin is metabolized. The end metabolites, which include 3 β -digoxigenin, 3-keto-digoxigenin, and their glucuronide and sulfate conjugates, are polar in nature and are postulated to be formed via hydrolysis, oxidation, and conjugation. The metabolism of digoxin is not dependent upon the cytochrome P-450 system, and digoxin is not known to induce or inhibit the cytochrome P-450 system.

Excretion: Elimination of digoxin follows first-order kinetics (that is, the quantity of digoxin eliminated at any time is proportional to the total body content). Following intravenous administration to healthy volunteers, 50% to 70% of a digoxin dose is excreted unchanged in the urine. Renal excretion of digoxin is proportional to glomerular filtration rate and is largely independent of urine flow. In healthy volunteers with normal renal function, digoxin has a half-life of 1.5 to 2.0 days. The half-life in anuric patients is prolonged to 3.5 to 5 days. Digoxin is not effectively removed from the body by dialysis, exchange transfusion, or during cardiopulmonary bypass because most of the drug is bound to tissue and does not circulate in the blood.

Special Populations: Race differences in digoxin pharmacokinetics have not been formally studied. Because digoxin is primarily eliminated as unchanged drug via the kidney and because there are no important differences in creatinine clearance among races, pharmacokinetic differences due to race are not expected.

The clearance of digoxin can be primarily correlated with renal function as indicated by creatinine clearance. In children with renal disease, digoxin must be carefully titrated based upon clinical response.

Plasma digoxin concentration profiles in patients with acute hepatitis generally fell within the range of profiles in a group of healthy subjects.

Pharmacodynamic and Clinical Effects:

The times to onset of pharmacologic effect and to peak effect of preparations of LANOXIN are shown in Table 2:

Table 2: Times to Onset of Pharmacologic Effect and to Peak Effect of Preparations of LANOXIN

Product	Time to Onset of Effect*	Time to Peak Effect*
LANOXIN Tablets	0.5 - 2 hours	2 - 6 hours
LANOXIN Elixir Pediatric	0.5 - 2 hours	2 - 6 hours
LANOXICAPS	0.5 - 2 hours	2 - 6 hours
LANOXIN Injection/IV	5 - 30 minutes†	1 - 4 hours

*Documented for ventricular response rate in atrial fibrillation, inotropic effects and electrocardiographic changes.

†Depending upon rate of infusion.

Hemodynamic Effects: Digoxin produces hemodynamic improvement in patients with heart failure. Short- and long-term therapy with the drug increases cardiac output and lowers pulmonary artery pressure, pulmonary capillary wedge pressure, and systemic vascular resistance. These hemodynamic effects are accompanied by an increase in the left ventricular ejection fraction and a decrease in end-systolic and end-diastolic dimensions.

Chronic Heart Failure: Two 12-week, double-blind, placebo-controlled studies enrolled 178 (RADIANCE trial) and 88 (PROVED trial) adult patients with NYHA class II or III heart failure previously treated with oral digoxin, a diuretic, and an ACE inhibitor (RADIANCE only) and randomized them to placebo or treatment with LANOXIN Tablets. Both trials demonstrated better preservation of exercise capacity in patients randomized to LANOXIN. Continued treatment with LANOXIN reduced the risk of developing worsening heart failure, as evidenced by heart failure-related hospitalizations and emergency care and the need for concomitant heart failure therapy. The larger study also showed treatment-related benefits in NYHA class and patients' global assessment. In the smaller trial, these trended in favor of a treatment benefit.

The Digitalis Investigation Group (DIG) main trial was a multicenter, randomized, double-blind, placebo-controlled mortality study of 6801 adult patients with heart failure and left ventricular ejection fraction ≤ 0.45 . At randomization, 67% were NYHA class I or II, 71% had heart failure of ischemic etiology, 44% had been receiving digoxin, and most were receiving concomitant ACE inhibitor (94%) and diuretic (82%). Patients were randomized to placebo or LANOXIN Tablets, the dose of which was adjusted for the patient's age, sex, lean body weight, and serum creatinine (see DOSAGE AND ADMINISTRATION), and followed for up to 58 months (median 37 months). The median daily dose prescribed was 0.25 mg. Overall all-cause mortality was 35% with no difference between groups (95% confidence limits for relative risk of 0.91 to 1.07). LANOXIN was associated with a 25% reduction in the number of hospitalizations for heart failure, a 28%

PRECAUTIONS:

Use in Patients with Impaired Renal Function: Digoxin is primarily excreted by the kidneys; therefore, patients with impaired renal function require smaller than usual maintenance doses of digoxin (see DOSAGE AND ADMINISTRATION). Because of the prolonged elimination half-life, a longer period of time is required to achieve an initial or new steady-state serum concentration in patients with renal impairment than in patients with normal renal function. If appropriate care is not taken to reduce the dose of digoxin, such patients are at high risk for toxicity, and toxic effects will last longer in such patients than in patients with normal renal function.

Use in Patients with Electrolyte Disorders: In patients with hypokalemia or hypomagnesemia, toxicity may occur despite serum digoxin concentrations below 2.0 ng/mL, because potassium or magnesium depletion sensitizes the myocardium to digoxin. Therefore, it is desirable to maintain normal serum potassium and magnesium concentrations in patients being treated with digoxin. Deficiencies of these electrolytes may result from malnutrition, diarrhea, or prolonged vomiting, as well as the use of the following drugs or procedures: diuretics, amphotericin B, corticosteroids, antacids, dialysis, and mechanical suction of gastrointestinal secretions.

Hypercalcemia from any cause predisposes the patient to digitalis toxicity. Calcium, particularly when administered rapidly by the intravenous route, may produce serious arrhythmias in digitalized patients. On the other hand, hypocalcemia can nullify the effects of digoxin in humans; thus, digoxin may be ineffective until serum calcium is restored to normal. These interactions are related to the fact that digoxin affects contractility and excitability of the heart in a manner similar to that of calcium.

Use in Thyroid Disorders and Hypermetabolic States: Hypothyroidism may reduce the requirements for digoxin. Heart failure and/or atrial arrhythmias resulting from hypermetabolic or hyperdynamic states (e.g., hyperthyroidism, hypoxia, or arteriovenous shunt) are best treated by addressing the underlying condition. Atrial arrhythmias associated with hypermetabolic states are particularly resistant to digoxin treatment. Care must be taken to avoid toxicity if digoxin is used.

Use in Patients with Acute Myocardial Infarction: Digoxin should be used with caution in patients with acute myocardial infarction. The use of inotropic drugs in some patients in this setting may result in undesirable increases in myocardial oxygen demand and ischemia.

Use During Electrical Cardioversion: It may be desirable to reduce the dose of digoxin for 1 to 2 days prior to electrical cardioversion of atrial fibrillation to avoid the induction of ventricular arrhythmias, but physicians must consider the consequences of increasing the ventricular response if digoxin is withdrawn. If digitalis toxicity is suspected, elective cardioversion should be delayed. If it is not prudent to delay cardioversion, the lowest possible energy level should be selected to avoid provoking ventricular arrhythmias.

Laboratory Test Monitoring: Patients receiving digoxin should have their serum electrolytes and renal function (serum creatinine concentrations) assessed periodically; the frequency of assessments will depend on the clinical setting. For discussion of serum digoxin concentrations, see DOSAGE AND ADMINISTRATION.

Drug Interactions: Potassium-depleting diuretics are a major contributing factor to digitalis toxicity. Calcium, particularly if administered rapidly by the intravenous route, may produce serious arrhythmias in digitalized patients. Quinidine, verapamil, amiodarone, propafenone, indomethacin, itraconazole, alprazolam, and spironolactone raise the serum digoxin concentration due to a reduction in clearance and/or volume of distribution of the drug, with the implication that digitalis intoxication may result. Erythromycin and clarithromycin (and possibly other macrolide antibiotics) and tetracycline may increase digoxin absorption in patients who inactivate digoxin by bacterial metabolism in the lower intestine, so that digitalis intoxication may result. Propantheline and diphenoxylate, by decreasing gut motility, may increase digoxin absorption. Antacids, kaolin-pectin, sulfasalazine, neomycin, cholestyramine, certain anticancer drugs, and metoclopramide may interfere with intestinal digoxin absorption, resulting in unexpectedly low serum concentrations. Rifampin may decrease serum digoxin concentration, especially in patients with renal dysfunction, by increasing the non-renal clearance of digoxin. There have been inconsistent reports regarding the effects of other drugs [e.g., quinine, penicillamine] on serum digoxin concentration. Thyroid administration to a digitalized, hypothyroid patient may increase the dose requirement of digoxin. Concomitant use of digoxin and sympathomimetics increases the risk of cardiac arrhythmias. Succinylcholine may cause a sudden extrusion of potassium from muscle cells, and may thereby cause arrhythmias in digitalized patients. Although beta-adrenergic blockers or calcium channel blockers and digoxin may be useful in combination to control atrial fibrillation, their additive effects on AV node conduction can result in advanced or complete heart block.

Due to the considerable variability of these interactions, dosage of digoxin should be individualized when patients receive these medications concurrently. Furthermore, caution should be exercised when combining digoxin with any drug that may cause a significant deterioration in renal function, since a decline in glomerular filtration or tubular secretion may impair the excretion of digoxin.

Drug/Laboratory Test Interactions: The use of therapeutic doses of digoxin may cause prolongation of the PR interval and depression of the ST segment on the electrocardiogram. Digoxin may produce false positive ST-T changes on the electrocardiogram during exercise testing. These electrophysiologic effects reflect an expected effect of the drug and are not indicative of toxicity.

Carcinogenesis, Mutagenesis, Impairment of Fertility: There have been no long-term studies performed in animals to evaluate carcinogenic potential, nor have studies been conducted to assess the mutagenic potential of digoxin or its potential to affect fertility.

Pregnancy: Teratogenic Effects: Pregnancy Category C. Animal reproduction studies have not been conducted with digoxin. It is also not known whether digoxin can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Digoxin should be given to a pregnant woman only if clearly needed.

Nursing Mothers: Studies have shown that digoxin concentrations in the mother's serum and milk are similar. However, the estimated exposure of a nursing infant to digoxin via breast feeding will be far below the usual infant maintenance dose. Therefore, this amount should have no pharmacologic effect upon the infant. Nevertheless, caution should be exercised when digoxin is administered to a nursing woman.

Pediatric Use: Newborn infants display considerable variability in their tolerance to digoxin. Premature and immature infants are particularly sensitive to the effects of digoxin, and the dosage of the drug must

LANOXIN® (digoxin) Injection Pediatric

not only be reduced but must be individualized according to their degree of maturity. Digitalis glycosides can cause poisoning in children due to accidental ingestion.

Geriatric Use: The majority of clinical experience gained with digoxin has been in the elderly population. This experience has not identified differences in response or adverse effects between the elderly and younger patients. However, this drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, which should be based on renal function, and it may be useful to monitor renal function.

ADVERSE REACTIONS: In general, the adverse reactions of digoxin are dose-dependent and occur at doses higher than those needed to achieve a therapeutic effect. Hence, adverse reactions are less common when digoxin is used within the recommended dose range or therapeutic serum concentration range and when there is careful attention to concurrent medications and conditions.

Because some patients may be particularly susceptible to side effects with digoxin, the dosage of the drug should always be selected carefully and adjusted as the clinical condition of the patient warrants. In the past, when high doses of digoxin were used and little attention was paid to clinical status or concurrent medications, adverse reactions to digoxin were more frequent and severe. Cardiac adverse reactions accounted for about one-half, gastrointestinal disturbances for about one-fourth, and CNS and other toxicity for about one-fourth of these adverse reactions. However, available evidence suggests that the incidence and severity of digoxin toxicity has decreased substantially in recent years. In recent controlled clinical trials, in patients with predominantly mild to moderate heart failure, the incidence of adverse experiences was comparable in patients taking digoxin and in those taking placebo. In a large mortality trial, the incidence of hospitalization for suspected digoxin toxicity was 2% in patients taking LANOXIN Tablets compared to 0.9% in patients taking placebo. In this trial, the most common manifestations of digoxin toxicity included gastrointestinal and cardiac disturbances; CNS manifestations were less common.

Adults: Cardiac: Therapeutic doses of digoxin may cause heart block in patients with pre-existing sinoatrial or AV conduction disorders; heart block can be avoided by adjusting the dose of digoxin. Prophylactic use of a cardiac pacemaker may be considered if the risk of heart block is considered unacceptable. High doses of digoxin may produce a variety of rhythm disturbances, such as first-degree, second-degree (Wenckebach), or third-degree heart block (including asystole); atrial tachycardia with block; AV dissociation; accelerated junctional (nodal) rhythm; unifocal or multifocal premature contractions (especially bigeminy or trigeminy); ventricular tachycardia; and ventricular fibrillation. Digoxin produces PR prolongation and ST segment depression which should not by themselves be considered digoxin toxicity. Cardiac toxicity can also occur at therapeutic doses in patients who have conditions which may alter their sensitivity to digoxin (see WARNINGS and PRECAUTIONS).

Gastrointestinal: Digoxin may cause anorexia, nausea, vomiting, and diarrhea. Rarely, the use of digoxin has been associated with abdominal pain, intestinal ischemia, and hemorrhagic necrosis of the intestines. **CNS:** Digoxin can produce visual disturbances (blurred or yellow vision), headache, weakness, dizziness, apathy, confusion, and mental disturbances (such as anxiety, depression, delirium, and hallucination).

Other: Gynecomastia has been occasionally observed following the prolonged use of digoxin. Thrombocytopenia and maculopapular rash and other skin reactions have been rarely observed.

The following table summarizes the incidence of those adverse experiences listed above for patients treated with LANOXIN Tablets or placebo from two randomized, double-blind, placebo-controlled withdrawal trials. Patients in these trials were also receiving diuretics with or without angiotensin-converting enzyme inhibitors. These patients had been stable on digoxin, and were randomized to digoxin or placebo. The results shown in Table 4 reflect the experience in patients following dosage titration with the use of serum digoxin concentrations and careful follow-up. These adverse experiences are consistent with results from a large, placebo-controlled mortality trial (DIG trial) wherein over half the patients were not receiving digoxin prior to enrollment.

Table 4: Adverse Experiences In Two Parallel, Double-Blind, Placebo-Controlled Withdrawal Trials (Number of Patients Reporting)

Adverse Experience	Digoxin Patients (n = 123)	Placebo Patients (n = 125)
Cardiac		
Palpitation	1	4
Ventricular extrasystole	1	1
Tachycardia	2	1
Heart arrest	1	1
Gastrointestinal		
Anorexia	1	4
Nausea	4	2
Vomiting	2	1
Diarrhea	4	1
Abdominal pain	0	6
CNS		
Headache	4	4
Dizziness	6	5
Mental disturbances	5	1
Other		
Rash	2	1

be clinically undesirable. Caution is thus advised and LANOXIN Injection Pediatric should probably be administered over a period of 5 minutes or longer. Mixing of LANOXIN Injection Pediatric with other drugs in the same container or simultaneous administration in the same intravenous line is not recommended.

In selecting a dose of digoxin, the following factors must be considered:

1. The body weight of the patient. Doses should be calculated based upon lean (i.e., ideal) body weight.
2. The patient's renal function, preferably evaluated on the basis of estimated creatinine clearance.
3. The patient's age. Infants and children require different doses of digoxin than adults. Also, advanced age may be indicative of diminished renal function even in patients with normal serum creatinine concentration (i.e., below 1.5 mg/dL).
4. Concomitant disease states, concurrent medications, or other factors likely to alter the pharmacokinetic or pharmacodynamic profile of digoxin (see PRECAUTIONS).

Serum Digoxin Concentrations: In general, the dose of digoxin used should be determined on clinical grounds. However, measurement of serum digoxin concentrations can be helpful to the clinician in determining the adequacy of digoxin therapy and in assigning certain probabilities to the likelihood of digoxin intoxication. About two-thirds of adults considered adequately digitalized (without evidence of toxicity) have serum digoxin concentrations ranging from 0.8 to 2.0 ng/mL. However, digoxin may produce clinical benefits even at serum concentrations below this range. About two-thirds of adult patients with clinical toxicity have serum digoxin concentrations greater than 2.0 ng/mL. However, since one-third of patients with clinical toxicity have concentrations less than 2.0 ng/mL, values below 2.0 ng/mL do not rule out the possibility that a certain sign or symptom is related to digoxin therapy. Rarely, there are patients who are unable to tolerate digoxin at serum concentrations below 0.8 ng/mL. Consequently, the serum concentration of digoxin should always be interpreted in the overall clinical context, and an isolated measurement should not be used alone as the basis for increasing or decreasing the dose of the drug.

To allow adequate time for equilibration of digoxin between serum and tissue, sampling of serum concentrations should be done just before the next scheduled dose of the drug. If this is not possible, sampling should be done at least 6 to 8 hours after the last dose, regardless of the route of administration or the formulation used. On a once-daily dosing schedule, the concentration of digoxin will be 10% to 25% lower when sampled at 24 versus 8 hours, depending upon the patient's renal function. On a twice-daily dosing schedule, there will be only minor differences in serum digoxin concentrations whether sampling is done at 8 or 12 hours after a dose.

If a discrepancy exists between the reported serum concentration and the observed clinical response, the clinician should consider the following possibilities:

1. Analytical problems in the assay procedure.
2. Inappropriate serum sampling time.
3. Administration of a digitalis glycoside other than digoxin.
4. Conditions (described in WARNINGS and PRECAUTIONS) causing an alteration in the sensitivity of the patient to digoxin.
5. Serum digoxin concentration may decrease acutely during periods of exercise without any associated change in clinical efficacy due to increased binding of digoxin to skeletal muscle.

Heart Failure: Adults: See the full prescribing information for LANOXIN Injection for specific recommendations.

Infants and Children: In general, divided daily dosing is recommended for infants and young children (under age 10). In the newborn period, renal clearance of digoxin is diminished and suitable dosage adjustments must be observed. This is especially pronounced in the premature infant. Beyond the immediate newborn period, children generally require proportionally larger doses than adults on the basis of body weight or body surface area. Children over 10 years of age require adult dosages in proportion to their body weight. Some researchers have suggested that infants and young children tolerate slightly higher serum concentrations than do adults.

Digitalization may be accomplished by either of two general approaches that vary in dosage and frequency of administration, but reach the same endpoint in terms of total amount of digoxin accumulated in the body.

1. If rapid digitalization is considered medically appropriate, it may be achieved by administering a loading dose based upon projected peak digoxin body stores. Maintenance dose can be calculated as a percentage of the loading dose.
2. More gradual digitalization may be obtained by beginning an appropriate maintenance dose, thus allowing digoxin body stores to accumulate slowly. Steady-state serum digoxin concentrations will be achieved in approximately five half-lives of the drug for the individual patient. Depending upon the patient's renal function, this will take between 1 and 3 weeks.

Rapid Digitalization with a Loading Dose: LANOXIN Injection Pediatric can be used to achieve rapid digitalization, with conversion to an oral formulation of LANOXIN for maintenance therapy. If patients are switched from intravenous to oral digoxin formulations, allowances must be made for differences in bioavailability when calculating maintenance dosages (see Table 1 in CLINICAL PHARMACOLOGY: Pharmacokinetics and dosing Table 5 below).

Intramuscular injection of digoxin is extremely painful and offers no advantages unless other routes of administration are contraindicated.

Peak digoxin body stores of 8 to 12 mcg/kg should provide therapeutic effect with minimum risk of toxicity in most patients with heart failure and normal sinus rhythm. Because of altered digoxin distribution and elimination, projected peak body stores for patients with renal insufficiency should be conservative (i.e., 6 to 10 mcg/kg) [see PRECAUTIONS].

Digitalizing and daily maintenance doses for each age group are given in Table 5 and should provide therapeutic effect with minimum risk of toxicity in most patients with heart failure and normal sinus rhythm.

Infants and Children: The side effects of digoxin in infants and children differ from those seen in adults in several respects. Although digoxin may produce anorexia, nausea, vomiting, diarrhea, and CNS disturbances in young patients, these are rarely the initial symptoms of overdosage. Rather, the earliest and most frequent manifestation of excessive dosing with digoxin in infants and children is the appearance of cardiac arrhythmias, including sinus bradycardia. In children, the use of digoxin may produce any arrhythmia. The most common are conduction disturbances or supraventricular tachyarrhythmias, such as atrial tachycardia (with or without block) and junctional (nodal) tachycardia. Ventricular arrhythmias are less common. Sinus bradycardia may be a sign of impending digoxin intoxication, especially in infants, even in the absence of first-degree heart block. Any arrhythmia or alteration in cardiac conduction that develops in a child taking digoxin should be assumed to be caused by digoxin, until further evaluation proves otherwise.

OVERDOSAGE:

Treatment of Adverse Reactions Produced by Overdosage: Digoxin should be temporarily discontinued until the adverse reaction resolves. Every effort should also be made to correct factors that may contribute to the adverse reaction (such as electrolyte disturbances or concurrent medications). Once the adverse reaction has resolved, therapy with digoxin may be reinstituted, following a careful reassessment of dose.

Withdrawal of digoxin may be all that is required to treat the adverse reaction. However, when the primary manifestation of digoxin overdosage is a cardiac arrhythmia, additional therapy may be needed.

If the rhythm disturbance is a symptomatic bradyarrhythmia or heart block, consideration should be given to the reversal of toxicity with DIGIBIND® [Digoxin Immune Fab (Ovine)] (see below), the use of atropine, or the insertion of a temporary cardiac pacemaker. However, asymptomatic bradycardia or heart block related to digoxin may require only temporary withdrawal of the drug and cardiac monitoring of the patient.

If the rhythm disturbance is a ventricular arrhythmia, consideration should be given to the correction of electrolyte disorders, particularly if hypokalemia (see below) or hypomagnesemia is present. DIGIBIND is a specific antidote for digoxin and may be used to reverse potentially life-threatening ventricular arrhythmias due to digoxin overdosage.

Administration of Potassium: Every effort should be made to maintain the serum potassium concentration between 4.0 and 5.5 mmol/L. Potassium is usually administered orally, but when correction of the arrhythmia is urgent and the serum potassium concentration is low, potassium may be administered cautiously by the intravenous route. The electrocardiogram should be monitored for any evidence of potassium toxicity (e.g., peaking of T waves) and to observe the effect on the arrhythmia. Potassium salts may be dangerous in patients who manifest bradycardia or heart block due to digoxin (unless primarily related to supraventricular tachycardia) and in the setting of massive digitalis overdosage (see Massive Digitalis Overdosage subsection).

Massive Digitalis Overdosage: Manifestations of life-threatening toxicity include ventricular tachycardia or ventricular fibrillation, or progressive bradyarrhythmias or heart block. The administration of more than 10 mg of digoxin in a previously healthy adult, or more than 4 mg in a previously healthy child, or a steady-state serum concentration greater than 10 ng/mL often results in cardiac arrest.

DIGIBIND should be used to reverse the toxic effects of ingestion of a massive overdose. The decision to administer DIGIBIND to a patient who has ingested a massive dose of digoxin but who has not yet manifested life-threatening toxicity should depend on the likelihood that life-threatening toxicity will occur (see above).

Patients with massive digitalis ingestion should receive large doses of activated charcoal to prevent absorption and bind digoxin in the gut during enteroenteric recirculation. Emesis or gastric lavage may be indicated especially if ingestion has occurred within 30 minutes of the patient's presentation at the hospital. Emesis should not be induced in patients who are obtunded. If a patient presents more than 2 hours after ingestion or already has toxic manifestations, it may be unsafe to induce vomiting or attempt passage of a gastric tube, because such maneuvers may induce an acute vagal episode that can worsen digitalis-related arrhythmias.

Severe digitalis intoxication can cause a massive shift of potassium from inside to outside the cell, leading to life-threatening hyperkalemia. The administration of potassium supplements in the setting of massive intoxication may be hazardous and should be avoided. Hyperkalemia caused by massive digitalis toxicity is best treated with DIGIBIND; initial treatment with glucose and insulin may also be required if hyperkalemia itself is acutely life-threatening.

DOSAGE AND ADMINISTRATION:

General: Recommended dosages of digoxin may require considerable modification because of individual sensitivity of the patient to the drug, the presence of associated conditions, or the use of concurrent medications.

Parenteral administration of digoxin should be used only when the need for rapid digitalization is urgent or when the drug cannot be taken orally. Intramuscular injection can lead to severe pain at the injection site, thus intravenous administration is preferred. If the drug must be administered by the intramuscular route, it should be injected deep into the muscle followed by massage. No more than 200 mcg (2 mL) should be injected into a single site.

LANOXIN Injection Pediatric can be administered undiluted or diluted with a 4-fold or greater volume of Sterile Water for Injection, 0.9% Sodium Chloride Injection, or 5% Dextrose Injection. The use of less than a 4-fold volume of diluent could lead to precipitation of the digoxin. Immediate use of the diluted product is recommended.

If tuberculin syringes are used to measure very small doses, one must be aware of the problem of inadvertent overdosage of digoxin. The syringe should not be flushed with the parenteral solution after its contents are expelled into an indwelling vascular catheter.

Slow infusion of LANOXIN Injection Pediatric is preferable to bolus administration. Rapid infusion of digitalis glycosides has been shown to cause systemic and coronary arteriolar constriction, which may

These recommendations assume the presence of normal renal function.

The loading dose should be administered in several portions, with roughly half the total given as the first dose. Additional fractions of this planned total dose may be given at 4- to 8-hour intervals, with careful assessment of clinical response before each additional dose. If the patient's clinical response necessitates a change from the calculated loading dose of digoxin, then calculation of the maintenance dose should be based upon the amount actually given.

Table 5: Usual Digitalizing and Maintenance Dosages for LANOXIN® Injection Pediatric in Children with Normal Renal Function Based on Lean Body Weight

Age	IV Digitalizing* Dose (mcg/kg)	Daily IV Maintenance Dose† (mcg/kg)
Premature	15 to 25	20% to 30% of the IV digitalizing dose‡
Full-Term	20 to 30	
1 to 24 Months	30 to 50	
2 to 5 Years	25 to 35	25% to 35% of the IV digitalizing dose‡
5 to 10 Years	15 to 30	
Over 10 Years	8 to 12	

*IV digitalizing doses are 80% of oral digitalizing doses.

†Divided daily dosing is recommended for children under 10 years of age.

‡Projected or actual digitalizing dose providing clinical response.

In children with renal disease, digoxin dosing must be carefully titrated based on clinical response.

Gradual Digitalization With A Maintenance Dose: More gradual digitalization can also be accomplished by beginning an appropriate maintenance dose. The range of percentages provided in Table 5 can be used in calculating this dose for patients with normal renal function.

It cannot be overemphasized that these pediatric dosage guidelines are based upon average patient response and substantial individual variation can be expected. Accordingly, ultimate dosage selection must be based upon clinical assessment of the patient.

Atrial Fibrillation: Peak digoxin body stores larger than the 8 to 12 mcg/kg required for most patients with heart failure and normal sinus rhythm have been used for control of ventricular rate in patients with atrial fibrillation. Doses of digoxin used for the treatment of chronic atrial fibrillation should be titrated to the minimum dose that achieves the desired ventricular rate control without causing undesirable side effects. Data are not available to establish the appropriate resting or exercise target rates that should be achieved.

Dosage Adjustment When Changing Preparations: The differences in bioavailability between injectable LANOXIN or LANOXICAPS and LANOXIN Elixir Pediatric or LANOXIN Tablets must be considered when changing patients from one dosage form to another.

Doses of 100 mcg (0.1 mg) and 200 mcg (0.2 mg) of LANOXICAPS are approximately equivalent to 125 mcg (0.125 mg) and 250 mcg (0.25 mg) doses of LANOXIN Tablets and Elixir Pediatric, respectively (see Table 1 in CLINICAL PHARMACOLOGY: Pharmacokinetics).

HOW SUPPLIED:

LANOXIN (digoxin) Injection Pediatric, 100 mcg (0.1 mg) in 1 mL; box of 10 ampuls (NDC 0173-0262-10).

Store at 15° to 25°C (59° to 77°F) and protect from light.

GlaxoWellcome

Manufactured by
Catalytic Pharmaceuticals, Inc.
Greenville, NC 27834
for Glaxo Wellcome Inc.
Research Triangle Park, NC 27709

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NDA 09-330

FINAL PRINTED LABELING

LANOXIN® (digoxin) Injection
Package InsertLabeling: original
NDA No: 9-330 Rec'd. 6-10-98
Reviewed by: Bauer
7/2/98

APPROVED

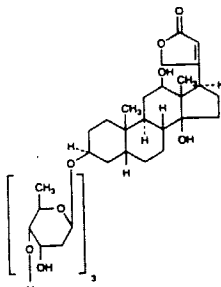
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PRODUCT INFORMATION

LANOXIN® (digoxin) Injection
500 mcg (0.5 mg) in 2 mL (250 mcg [0.25 mg] per mL)

DESCRIPTION: LANOXIN (digoxin) is one of the cardiac (or digitalis) glycosides, a closely related group of drugs having in common specific effects on the myocardium. These drugs are found in a number of plants. Digoxin is extracted from the leaves of *Digitalis lanata*. The term "digitalis" is used to designate the whole group of glycosides. The glycosides are composed of two portions: a sugar and a cardenolide (hence "glycosides").

Digoxin is described chemically as (3 β ,5 β ,12 β)-3-[(2,6-dideoxy- β -D-ribo-hexopyranosyl)-(1 \rightarrow 4)-O-2,6-dideoxy- β -D-ribo-hexopyranosyl-(1 \rightarrow 4)-2,6-dideoxy- β -D-ribo-hexopyranosyl]oxy]-12,14-dihydroxy-card-20(22)-enolide. Its molecular formula is C₄₁H₆₄O₁₄, its molecular weight is 780.95, and its structural formula is:



Digoxin exists as odorless white crystals that melt with decomposition above 230°C. The drug is practically insoluble in water and in ether; slightly soluble in diluted (50%) alcohol and in chloroform; and freely soluble in pyridine.

LANOXIN Injection is a sterile solution of digoxin for intravenous injection. The vehicle contains 40% propylene glycol and 10% alcohol. The injection is buffered to a pH of 6.8 to 7.2 with 0.17% sodium phosphate and 0.08% anhydrous citric acid. Each 2-mL ampul contains 500 mcg (0.5 mg) digoxin (250 mcg [0.25 mg] per mL). Dilution is not required.

CLINICAL PHARMACOLOGY:

Mechanism of Action: Digoxin inhibits sodium-potassium ATPase, an enzyme that regulates the quantity of sodium and potassium inside cells. Inhibition of the enzyme leads to an increase in the intracellular concentration of sodium and thus (by stimulation of sodium-calcium exchange) an increase in the intracellular concentration of calcium. The beneficial effects of digoxin result from direct actions on cardiac muscle, as well as indirect actions on the cardiovascular system mediated by effects on the autonomic nervous system. The autonomic effects include: (1) a vagomimetic action, which is responsible for the effects of digoxin on the sinoatrial and atrioventricular (AV) nodes; and (2) baroreceptor sensitization, which results in increased afferent inhibitory activity and reduced activity of the sympathetic nervous system and renin-angiotensin system for any given increment in mean arterial pressure. The pharmacologic consequences of these direct and indirect effects are: (1) an increase in the force and velocity of myocardial systolic contraction (positive inotropic action); (2) a decrease in the degree of activation of the sympathetic nervous system and renin-angiotensin system (neurohormonal deactivating effect); and (3) slowing of the heart rate and decreased conduction velocity through the AV node (vagomimetic effect). The effects of digoxin in heart failure are mediated by its positive inotropic and neurohormonal deactivating effects, whereas the effects of the drug in atrial arrhythmias are related to its vagomimetic actions. In high doses, digoxin increases sympathetic outflow from the central nervous system (CNS). This increase in sympathetic activity may be an important factor in digitalis toxicity.

Pharmacokinetics: Note: the following data are from studies performed in adults, unless otherwise stated.

Absorption: Comparisons of the systemic availability and equivalent doses for preparations of LANOXIN are shown in Table 1:

Table 1: Comparisons of the Systemic Availability and Equivalent Doses for Preparations of LANOXIN

Product	Absolute Bioavailability	Equivalent Doses (mcg)* Among Dosage Forms			
LANOXIN Tablets	60 - 80%	62.5	125	250	500
LANOXIN Elixir Pediatric	70 - 85%	62.5	125	250	500
LANOXICAPS®	90 - 100%	50	100	200	400
LANOXIN Injection/IV	100%	50	100	200	400

Use of LANOXIN was associated with a trend in reduction in time to all-cause death or hospitalization. The trend was evident in subgroups of patients with mild heart failure as well as more severe disease, as shown in Table 3. Although the effect on all-cause death or hospitalization was not statistically significant, much of the apparent benefit derived from effects on mortality and hospitalization attributed to heart failure.

Table 3: Subgroup Analyses of Mortality and Hospitalization During the First Two Years Following Randomization

	n	Risk of All-Cause Mortality or All-Cause Hospitalization*			Risk of HF-Related Mortality or HF-Related Hospitalization*		
		Placebo	LANOXIN	Relative risk†	Placebo	LANOXIN	Relative risk†
All patients (EF \leq 0.45)	6801	604	593	0.94 (0.88-1.00)	294	217	0.69 (0.63-0.76)
NYHA I/II	4571	549	541	0.96 (0.89-1.04)	242	178	0.70 (0.62-0.80)
EF 0.25-0.45	4543	568	571	0.99 (0.91-1.07)	244	190	0.74 (0.66-0.84)
CTR \leq 0.55	4455	561	563	0.98 (0.91-1.06)	239	180	0.71 (0.63-0.81)
NYHA III/IV	2224	719	696	0.88 (0.80-0.97)	402	295	0.65 (0.57-0.75)
EF $<$ 0.25	2258	677	637	0.84 (0.76-0.93)	394	270	0.61 (0.53-0.71)
CTR $>$ 0.55	2346	687	650	0.85 (0.77-0.94)	398	287	0.65 (0.57-0.75)
EF $>$ 0.45‡	987	571	585	1.04 (0.88-1.23)	179	136	0.72 (0.53-0.99)

* Number of patients with an event during the first 2 years per 1000 randomized patients.

† Relative risk (95% confidence interval).

‡ DIG Ancillary Study.

In situations where there is no statistically significant benefit of treatment evident from a trial's primary endpoint, results pertaining to a secondary endpoint should be interpreted cautiously.

Chronic Atrial Fibrillation: In patients with chronic atrial fibrillation, digoxin slows rapid ventricular response rate in a linear dose-response fashion from 0.25 to 0.75 mg/day. Digoxin should not be used for the treatment of multifocal atrial tachycardia.

INDICATIONS AND USAGE:

Heart Failure: LANOXIN is indicated for the treatment of mild to moderate heart failure. LANOXIN increases left ventricular ejection fraction and improves heart failure symptoms as evidenced by exercise capacity and heart failure-related hospitalizations and emergency care, while having no effect on mortality. Where possible, LANOXIN should be used with a diuretic and an angiotensin-converting enzyme inhibitor, but an optimal order for starting these three drugs cannot be specified.

Atrial Fibrillation: LANOXIN is indicated for the control of ventricular response rate in patients with chronic atrial fibrillation.

CONTRAINDICATIONS: Digitalis glycosides are contraindicated in patients with ventricular fibrillation or in patients with a known hypersensitivity to digoxin. A hypersensitivity reaction to other digitalis preparations usually constitutes a contraindication to digoxin.

WARNINGS: Sinoatrial Node Disease and AV Block: Because digoxin slows sinoatrial and AV conduction, the drug commonly prolongs the PR interval. The drug may cause severe sinus bradycardia or sinoatrial block in patients with pre-existing sinus node disease and may cause advanced or complete heart block in patients with pre-existing incomplete AV block. In such patients consideration should be given to the insertion of a pacemaker before treatment with digoxin.

Accessory AV Pathway (Wolff-Parkinson-White Syndrome): After intravenous digoxin therapy, some patients with paroxysmal atrial fibrillation or flutter and a coexisting accessory AV pathway have developed increased antegrade conduction across the accessory pathway bypassing the AV node, leading to a very rapid ventricular response or ventricular fibrillation. Unless conduction down the accessory pathway has been blocked (either pharmacologically or by surgery), digoxin should not be used in such patients. The treatment of paroxysmal supraventricular tachycardia in such patients is usually direct-current cardioversion.

Use in Patients with Preserved Left Ventricular Systolic Function: Patients with certain disorders involving heart failure associated with preserved left ventricular ejection fraction may be particularly susceptible to toxicity of the drug. Such disorders include restrictive cardiomyopathy, constrictive pericarditis, amyloid heart disease, and acute or pulmonary. Patients with idiopathic hypertrophic subaortic stenosis may have worsening of the outflow obstruction due to the inotropic effects of digoxin.

PRECAUTIONS:

Use in Patients with Impaired Renal Function: Digoxin is primarily excreted by the kidneys; therefore, patients with impaired renal function require smaller than usual maintenance doses of digoxin (see DOSAGE AND ADMINISTRATION). Because of the prolonged elimination half-life, a longer period of time is required to achieve an initial or new steady-state serum concentration in patients with renal impairment than in patients with normal renal function.

LANOXIN Tablets are equivalent to 100 mcg LANOXIN Injection/IV.

Distribution: Following drug administration, a 6- to 8-hour tissue distribution phase is observed. This is followed by a much more gradual decline in the serum concentration of the drug, which is dependent on the elimination of digoxin from the body. The peak height and slope of the early portion (absorption/distribution phases) of the serum concentration-time curve are dependent upon the route of administration and the absorption characteristics of the formulation. Clinical evidence indicates that the early high serum concentrations do not reflect the concentration of digoxin at its site of action, but that with chronic use, the steady-state post-distribution serum concentrations are in equilibrium with tissue concentrations and correlate with pharmacologic effects. In individual patients, these post-distribution serum concentrations may be useful in evaluating therapeutic and toxic effects (see DOSAGE AND ADMINISTRATION: Serum Digoxin Concentrations).

Digoxin is concentrated in tissues and therefore has a large apparent volume of distribution. Digoxin crosses both the blood-brain barrier and the placenta. At delivery, the serum digoxin concentration in the newborn is similar to the serum concentration in the mother. Approximately 25% of digoxin in the plasma is bound to protein. Serum digoxin concentrations are not significantly altered by large changes in fat tissue weight, so that its distribution space correlates best with lean (i.e., ideal) body weight, not total body weight.

Metabolism: Only a small percentage (16%) of a dose of digoxin is metabolized. The end metabolites, which include 3 β -digoxigenin, 3-keto-digoxigenin, and their glucuronide and sulfate conjugates, are polar in nature and are postulated to be formed via hydrolysis, oxidation, and conjugation. The metabolism of digoxin is not dependent upon the cytochrome P-450 system, and digoxin is not known to induce or inhibit the cytochrome P-450 system.

Excretion: Elimination of digoxin follows first-order kinetics (that is, the quantity of digoxin eliminated at any time is proportional to the total body content). Following intravenous administration to healthy volunteers, 50% to 70% of a digoxin dose is excreted unchanged in the urine. Renal excretion of digoxin is proportional to glomerular filtration rate and is largely independent of urine flow. In healthy volunteers with normal renal function, digoxin has a half-life of 1.5 to 2.0 days. The half-life in anuric patients is prolonged to 3.5 to 5 days. Digoxin is not effectively removed from the body by dialysis, exchange transfusion, or during cardiopulmonary bypass because most of the drug is bound to tissue and does not circulate in the blood.

Special Populations: Race differences in digoxin pharmacokinetics have not been formally studied. Because digoxin is primarily eliminated as unchanged drug via the kidney and because there are no important differences in creatinine clearance among races, pharmacokinetic differences due to race are not expected.

The clearance of digoxin can be primarily correlated with renal function as indicated by creatinine clearance. The Cockcroft and Gault formula for estimation of creatinine clearance includes age, body weight, and gender. A table that provides the usual daily maintenance dose requirements of LANOXIN Tablets based on creatinine clearance (per 70 kg) is presented in the DOSAGE AND ADMINISTRATION section.

Plasma digoxin concentration profiles in patients with acute hepatitis generally fell within the range of profiles in a group of healthy subjects.

Pharmacodynamic and Clinical Effects: The times to onset of pharmacologic effect and to peak effect of preparations of LANOXIN are shown in Table 2:

Table 2: Times to Onset of Pharmacologic Effect and to Peak Effect of Preparations of LANOXIN

Product	Time to Onset of Effect*	Time to Peak Effect*
LANOXIN Tablets	0.5 - 2 hours	2 - 6 hours
LANOXIN Elixir Pediatric	0.5 - 2 hours	2 - 6 hours
LANOXIN CAPS	0.5 - 2 hours	2 - 6 hours
LANOXIN Injection/IV	5 - 30 minutes†	1 - 4 hours

* Documented for ventricular response rate in atrial fibrillation, inotropic effects and electrocardiographic changes.
† Depending upon rate of infusion.

Hemodynamic Effects: Digoxin produces hemodynamic improvement in patients with heart failure. Short- and long-term therapy with the drug increases cardiac output and lowers pulmonary artery pressure, pulmonary capillary wedge pressure, and systemic vascular resistance. These hemodynamic effects are accompanied by an increase in the left ventricular ejection fraction and a decrease in end-systolic and end-diastolic dimensions.

Chronic Heart Failure: Two 12-week, double-blind, placebo-controlled studies enrolled 178 (RADIANCE trial) and 88 (PROVED trial) patients with NYHA class II or III heart failure previously treated with oral digoxin, a diuretic, and an ACE inhibitor (RADIANCE only) and randomized them to placebo or treatment with LANOXIN Tablets. Both trials demonstrated better preservation of exercise capacity in patients randomized to LANOXIN. Continued treatment with LANOXIN reduced the risk of developing worsening heart failure, as evidenced by heart failure-related hospitalizations and emergency care and the need for concomitant heart failure therapy. The larger study also showed treatment-related benefits in NYHA class and patients' global assessment. In the smaller trial, these trends in favor of a treatment benefit.

The Digitalis Investigation Group (DIG) main trial was a multicenter, randomized, double-blind, placebo-controlled mortality study of 6801 patients with heart failure and left ventricular ejection fraction ≤ 0.45 . At randomization, 67% were NYHA class I or II, 71% had heart failure of ischemic etiology, 44% had been receiving digoxin, and most were receiving concomitant ACE inhibitor (94%) and diuretic (82%). Patients were randomized to placebo or LANOXIN Tablets, the dose of which was adjusted for the patient's age, sex, lean body weight, and serum creatinine (see DOSAGE AND ADMINISTRATION), and followed for up to 58 months (median 37 months). The median daily dose prescribed was 0.25 mg. Overall all-cause mortality was 35% with no difference between groups (95% confidence limits for relative risk of 0.91 to 1.07). LANOXIN was associated with a 25% reduction in the number of hospitalizations for heart failure, a 28% reduction in the risk of a patient having at least one hospitalization for heart failure, and a 6.5% reduction in total hospitalizations (for any cause).

tion. If appropriate care is not taken to reduce the dose of digoxin, such patients are at high risk for toxicity, and toxic effects will last longer in such patients than in patients with normal renal function.

Use in Patients with Electrolyte Disorders: In patients with hypokalemia or hypomagnesemia, toxicity may occur despite serum digoxin concentrations below 2.0 ng/mL, because potassium or magnesium depletion sensitizes the myocardium to digoxin. Therefore, it is desirable to maintain normal serum potassium and magnesium concentrations in patients being treated with digoxin. Deficiencies of these electrolytes may result from malnutrition, diarrhea, or prolonged vomiting, as well as the use of the following drugs or procedures: diuretics, amphotericin B, corticosteroids, antacids, dialysis, and mechanical suction of gastrointestinal secretions.

Hypercalcemia from any cause predisposes the patient to digitalis toxicity. Calcium, particularly when administered rapidly by the intravenous route, may produce serious arrhythmias in digitalized patients. On the other hand, hypocalcemia can nullify the effects of digoxin in humans; thus, digoxin may be ineffective until serum calcium is restored to normal. These interactions are related to the fact that digoxin affects contractility and excitability of the heart in a manner similar to that of calcium.

Use in Thyroid Disorders and Hypermetabolic States: Hypothyroidism may reduce the requirements for digoxin. Heart failure and/or atrial arrhythmias resulting from hypermetabolic or hyperdynamic states (e.g., hyperthyroidism, hypoxia, or arteriovenous shunt) are best treated by addressing the underlying condition. Atrial arrhythmias associated with hypermetabolic states are particularly resistant to digoxin treatment. Care must be taken to avoid toxicity if digoxin is used.

Use in Patients with Acute Myocardial Infarction: Digoxin should be used with caution in patients with acute myocardial infarction. The use of inotropic drugs in some patients in this setting may result in undesirable increases in myocardial oxygen demand and ischemia.

Use During Electrical Cardioversion: It may be desirable to reduce the dose of digoxin for 1 to 2 days prior to electrical cardioversion of atrial fibrillation to avoid the induction of ventricular arrhythmias, but physicians must consider the consequences of increasing the ventricular response if digoxin is withdrawn. If digitalis toxicity is suspected, elective cardioversion should be delayed. If it is not prudent to delay cardioversion, the lowest possible energy level should be selected to avoid provoking ventricular arrhythmias.

Laboratory Test Monitoring: Patients receiving digoxin should have their serum electrolytes and renal function (serum creatinine concentrations) assessed periodically; the frequency of assessments will depend on the clinical setting. For discussion of serum digoxin concentrations, see DOSAGE AND ADMINISTRATION.

Drug Interactions: Potassium-depleting diuretics are a major contributing factor to digitalis toxicity. Calcium, particularly if administered rapidly by the intravenous route, may produce serious arrhythmias in digitalized patients. Quinidine, verapamil, amiodarone, propafenone, indomethacin, itraconazole, alprazolam, and spironolactone raise the serum digoxin concentration due to a reduction in clearance and/or in volume of distribution of the drug, with the implication that digitalis intoxication may result. Erythromycin and clarithromycin (and possibly other macrolide antibiotics) and tetracycline may increase digoxin absorption in patients who inactivate digoxin by bacterial metabolism in the lower intestine, so that digitalis intoxication may result. Propantheline and diphenoxylate, by decreasing gut motility, may increase digoxin absorption. Antacids, kaolin-pectin, sulfasalazine, neomycin, cholestyramine, certain anticancer drugs, and metoclopramide may interfere with intestinal digoxin absorption, resulting in unexpectedly low serum concentrations. Rifampin may decrease serum digoxin concentration, especially in patients with renal dysfunction, by increasing the non-renal clearance of digoxin. There have been inconsistent reports regarding the effects of other drugs (e.g., quinine, penicillamine) on serum digoxin concentration. Thyroid administration to a digitalized, hypothyroid patient may increase the dose requirement of digoxin. Concomitant use of digoxin and sympathomimetics increases the risk of cardiac arrhythmias. Succinylcholine may cause a sudden extrusion of potassium from muscle cells, and may thereby cause arrhythmias in digitalized patients. Although beta-adrenergic blockers or calcium channel blockers and digoxin may be useful in combination to control atrial fibrillation, their additive effects on AV node conduction can result in advanced or complete heart block.

Due to the considerable variability of these interactions, the dosage of digoxin should be individualized when patients receive these medications concurrently. Furthermore, caution should be exercised when combining digoxin with any drug that may cause a significant deterioration in renal function, since a decline in glomerular filtration or tubular secretion may impair the excretion of digoxin.

Drug/Laboratory Test Interactions: The use of therapeutic doses of digoxin may cause prolongation of the PR interval and depression of the ST segment on the electrocardiogram. Digoxin may produce false positive ST-T changes on the electrocardiogram during exercise testing. These electrophysiologic effects reflect an expected effect of the drug and are not indicative of toxicity.

Carcinogenesis, Mutagenesis, Impairment of Fertility: There have been no long-term studies performed in animals to evaluate carcinogenic potential, nor have studies been conducted to assess the mutagenic potential of digoxin or its potential to affect fertility.

Pregnancy: Teratogenic Effects: Pregnancy Category C. Animal reproduction studies have not been conducted with digoxin. It is also not known whether digoxin can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Digoxin should be given to a pregnant woman only if clearly needed.

Nursing Mothers: Studies have shown that digoxin concentrations in the mother's serum and milk are similar. However, the estimated exposure of a nursing infant to digoxin via breast feeding will be far below the usual infant maintenance dose. Therefore, this amount should have no pharmacologic effect upon the infant. Nevertheless, caution should be exercised when digoxin is administered to a nursing woman.

Pediatric Use: Newborn infants display considerable variability in their tolerance to digoxin. Premature and immature infants are particularly sensitive to the effects of digoxin, and the dosage of the drug must not only be reduced but must be individualized according to their degree of maturity. Digitalis glycosides can cause poisoning in children due to accidental ingestion.

Geriatric Use: The majority of clinical experience gained with digoxin has been in the elderly population. This experience has not identified differences in response or adverse effects between the elderly and younger patients. However, this drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, which should be based on renal function, and it may be useful to monitor renal function (see DOSAGE AND ADMINISTRATION).

LANOXIN® (digoxin) Injection

ADVERSE REACTIONS: In general, the adverse reactions of digoxin are dose-dependent and occur at doses higher than those needed to achieve a therapeutic effect. Hence, adverse reactions are less common when digoxin is used within the recommended dose range or therapeutic serum concentration range and when there is careful attention to concurrent medications and conditions.

Because some patients may be particularly susceptible to side effects with digoxin, the dosage of the drug should always be selected carefully and adjusted as the clinical condition of the patient warrants. In the past, when high doses of digoxin were used and little attention was paid to clinical status or concurrent medications, adverse reactions to digoxin were more frequent and severe. Cardiac adverse reactions accounted for about one-half, gastrointestinal disturbances for about one-fourth, and CNS and other toxicity for about one-fourth of these adverse reactions. However, available evidence suggests that the incidence and severity of digoxin toxicity has decreased substantially in recent years. In recent controlled clinical trials, in patients with predominantly mild to moderate heart failure, the incidence of adverse experiences was comparable in patients taking digoxin and in those taking placebo. In a large mortality trial, the incidence of hospitalization for suspected digoxin toxicity was 2% in patients taking LANOXIN Tablets compared to 0.9% in patients taking placebo. In this trial, the most common manifestations of digoxin toxicity included gastrointestinal and cardiac disturbances; CNS manifestations were less common.

Adults: Cardiac: Therapeutic doses of digoxin may cause heart block in patients with pre-existing sinoatrial or AV conduction disorders; heart block can be avoided by adjusting the dose of digoxin. Prophylactic use of a cardiac pacemaker may be considered if the risk of heart block is considered unacceptable. High doses of digoxin may produce a variety of rhythm disturbances, such as first-degree, second-degree (Wenckebach), or third-degree heart block (including asystole); atrial tachycardia with block; AV dissociation; accelerated junctional (nodal) rhythm; unifocal or multifocal premature contractions (especially bigeminy or trigeminy); ventricular tachycardia; and ventricular fibrillation. Digoxin produces PR prolongation and ST segment depression which should not be themselves be considered digoxin toxicity. Cardiac toxicity can also occur at therapeutic doses in patients who have conditions which may alter their sensitivity to digoxin (see WARNINGS and PRECAUTIONS).

Gastrointestinal: Digoxin may cause anorexia, nausea, vomiting, and diarrhea. Rarely, the use of digoxin has been associated with abdominal pain, intestinal ischemia, and hemorrhagic necrosis of the intestines.

CNS: Digoxin can produce visual disturbances (blurred or yellow vision), headache, weakness, dizziness, apathy, confusion, and mental disturbances (such as anxiety, depression, delirium, and hallucination).

Other: Gynecomastia has been occasionally observed following the prolonged use of digoxin. Thrombocytopenia and maculopapular rash and other skin reactions have been rarely observed.

The following table summarizes the incidence of those adverse experiences listed above for patients treated with LANOXIN Tablets or placebo from two randomized, double-blind, placebo-controlled withdrawal trials. Patients in these trials were also receiving diuretics with or without angiotensin-converting enzyme inhibitors. These patients had been stable on digoxin, and were randomized to digoxin or placebo. The results shown in Table 4 reflect the experience in patients following dosage titration with the use of serum digoxin concentrations and careful follow-up. These adverse experiences are consistent with results from a large, placebo-controlled mortality trial (DIG trial) wherein over half the patients were not receiving digoxin prior to enrollment.

Table 4: Adverse Experiences in Two Parallel, Double-Blind, Placebo-Controlled Withdrawal Trials (Number of Patients Reporting)

Adverse Experience	Digoxin Patients (n = 123)	Placebo Patients (n = 125)
Cardiac		
Palpitation	1	4
Ventricular extrasystole	1	1
Tachycardia	2	1
Heart arrest	1	1
Gastrointestinal		
Anorexia	1	4
Nausea	4	2
Vomiting	2	1
Diarrhea	4	1
Abdominal pain	0	6
CNS		
Headache	4	4
Dizziness	6	5
Mental disturbances	5	1
Other		
Rash	2	1
Death	4	3

Infants and Children: The side effects of digoxin in infants and children differ from those seen in adults in several respects. Although digoxin may produce anorexia, nausea, vomiting, diarrhea, and CNS disturbances in young patients, these are rarely the initial symptoms of overdosage. Rather, the earliest and most frequent manifestation of excessive dosing with digoxin in infants and children is the appearance of cardiac arrhythmias, including sinus bradycardia. In children, the use of digoxin may produce atrial arrhythmia. The most common are conduction disturbances or supraventricular tachyarrhythmias, such as atrial tachycardia (with or without block) and junctional (nodal) tachycardia. Ventricular arrhythmias are less common. Sinus bradycardia may be a sign of impending

this range. About two-thirds of adult patients with clinical toxicity have serum digoxin concentrations greater than 2.0 ng/mL. However, since one-third of patients with clinical toxicity have concentrations less than 2.0 ng/mL, values below 2.0 ng/mL do not rule out the possibility that a certain sign or symptom is related to digoxin therapy. Rarely, there are patients who are unable to tolerate digoxin at serum concentrations below 0.8 ng/mL. Consequently, the serum concentration of digoxin should always be interpreted in the overall clinical context, and an isolated measurement should not be used alone as the basis for increasing or decreasing the dose of the drug.

To allow adequate time for equilibration of digoxin between serum and tissue, sampling of serum concentrations should be done just before the next scheduled dose of the drug. If this is not possible, sampling should be done at least 6 to 8 hours after the last dose, regardless of the route of administration or the formulation used. On a once-daily dosing schedule, the concentration of digoxin will be 10% to 25% lower when sampled at 24 versus 8 hours, depending upon the patient's renal function. On a twice-daily dosing schedule, there will be only minor differences in serum digoxin concentrations whether sampling is done at 8 or 12 hours after a dose.

If a discrepancy exists between the reported serum concentration and the observed clinical response, the clinician should consider the following possibilities:

1. Analytical problems in the assay procedure.
2. Inappropriate serum sampling time.
3. Administration of a digitalis glycoside other than digoxin.
4. Conditions (described in WARNINGS and PRECAUTIONS) causing an alteration in the sensitivity of the patient to digoxin.
5. Serum digoxin concentration may decrease acutely during periods of exercise without any associated change in clinical efficacy due to increased binding of digoxin to skeletal muscle.

Heart Failure: Adults: Digitalization may be accomplished by either of two general approaches that vary in dosage and frequency of administration, but reach the same endpoint in terms of total amount of digoxin accumulated in the body.

1. If rapid digitalization is considered medically appropriate, it may be achieved by administering a loading dose based upon projected peak digoxin body stores. Maintenance dose can be calculated as a percentage of the loading dose.
2. More gradual digitalization may be obtained by beginning an appropriate maintenance dose, thus allowing digoxin body stores to accumulate slowly. Steady-state serum digoxin concentrations will be achieved in approximately five half-lives of the drug for the individual patient. Depending upon the patient's renal function, this will take between 1 and 3 weeks.

Rapid Digitalization with a Loading Dose: LANOXIN Injection is frequently used to achieve rapid digitalization, with conversion to LANOXIN Tablets or LANOXICAPS for maintenance therapy. If patients are switched from intravenous to oral digoxin formulations, allowances must be made for differences in bioavailability when calculating maintenance dosages (see Table 1, CLINICAL PHARMACOLOGY: Pharmacokinetics and dosing Table 5 below).

Intramuscular injection of digoxin is extremely painful and offers no advantages unless other routes of administration are contraindicated.

Peak digoxin body stores of 8 to 12 mcg/kg should provide therapeutic effect with minimum risk of toxicity in most patients with heart failure and normal sinus rhythm. Because of altered digoxin distribution and elimination, projected peak body stores for patients with renal insufficiency should be conservative (i.e., 6 to 10 mcg/kg) [see PRECAUTIONS].

The loading dose should be administered in several portions, with roughly half the total given as the first dose. Additional fractions of this planned total dose may be given at 6- to 8-hour intervals, with careful assessment of clinical response before each additional dose. If the patient's clinical response necessitates a change from the calculated loading dose of digoxin, then calculation of the maintenance dose should be based upon the amount actually given.

A single initial intravenous dose of 400 to 600 mcg (0.4 to 0.6 mg) of LANOXIN Injection usually produces a detectable effect in 5 to 30 minutes that becomes maximal in 1 to 4 hours. Additional doses of 100 to 300 mcg (0.1 to 0.3 mg) may be given cautiously at 6- to 8-hour intervals until clinical evidence of an adequate effect is noted. The usual amount of LANOXIN Injection that a 70-kg patient requires to achieve 8- to 12-mcg/kg peak body stores is 800 to 1000 mcg (0.8 to 1.0 mg).

Maintenance Dosing: The doses of oral digoxin used in controlled trials in patients with heart failure have ranged from 125 to 500 mcg (0.125 to 0.5 mg) once daily. In these studies, the digoxin dose has been generally titrated according to the patient's age, lean body weight, and renal function. Therapy is generally initiated at a dose of 250 mcg (0.25 mg) once daily in patients under age 70 with good renal function, at a dose of 125 mcg (0.125 mg) once daily in patients over age 70 or with impaired renal function, and at a dose of 62.5 mcg (0.0625 mg) in patients with marked renal impairment. Doses may be increased every 2 weeks according to clinical response.

In a subset of approximately 1800 patients enrolled in the DIG trial (wherein dosing was based on an algorithm similar to that in Table 5) the mean (± SD) serum digoxin concentrations at 1 month and 12 months were 1.01 ± 0.47 ng/mL and 0.97 ± 0.43 ng/mL, respectively.

The maintenance dose should be based upon the percentage of the peak body stores lost each day through elimination. The following formula has had wide clinical use:

$$\text{Maintenance Dose} = \text{Peak Body Stores (i.e., Loading Dose)} \times \% \text{ Daily Loss}/100$$

$$\text{Where: } \% \text{ Daily Loss} = 14 + \text{Ccr}/5$$

(Ccr is creatinine clearance, corrected to 70 kg body weight or 1.73 m² body surface area.)

Table 5 provides average daily maintenance dose requirements of LANOXIN Injection for patients with heart failure based upon lean body weight and renal function:

Table 5: Usual Daily Maintenance Dose Requirements (mcg) of LANOXIN Injection for Estimated Peak Body Stores of 10 mcg/kg*

	Lean Body Weight
--	------------------

digoxin intoxication, especially in infants, even in the absence of first-degree heart block. Any arrhythmia of alteration in cardiac conduction that develops in a child taking digoxin should be assumed to be caused by digoxin, until further evaluation proves otherwise.

OVERDOSAGE:

Treatment of Adverse Reactions Produced by Overdosage: Digoxin should be temporarily discontinued until the adverse reaction resolves. Every effort should also be made to correct factors that may contribute to the adverse reaction (such as electrolyte disturbances or concurrent medications). Once the adverse reaction has resolved, therapy with digoxin may be reinstituted, following a careful reassessment of dose.

Withdrawal of digoxin may be all that is required to treat the adverse reaction. However, when the primary manifestation of digoxin overdosage is a cardiac arrhythmia, additional therapy may be needed.

If the rhythm disturbance is a symptomatic bradyarrhythmia or heart block, consideration should be given to the reversal of toxicity with DIGIBIND® [Digoxin Immune Fab (Ovine)] (see below), the use of atropine, or the insertion of a temporary cardiac pacemaker. However, asymptomatic bradycardia or heart block related to digoxin may require only temporary withdrawal of the drug and cardiac monitoring of the patient.

If the rhythm disturbance is a ventricular arrhythmia, consideration should be given to the correction of electrolyte disorders, particularly if hypokalemia (see below) or hypomagnesemia is present. DIGIBIND is a specific antidote for digoxin and may be used to reverse potentially life-threatening ventricular arrhythmias due to digoxin overdosage.

Administration of Potassium: Every effort should be made to maintain the serum potassium concentration between 4.0 and 5.5 mmol/L. Potassium is usually administered orally, but when correction of the arrhythmia is urgent and the serum potassium concentration is low, potassium may be administered cautiously by the intravenous route. The electrocardiogram should be monitored for any evidence of potassium toxicity (e.g., peaking of T waves) and to observe the effect on the arrhythmia. Potassium salts may be dangerous in patients who manifest bradycardia or heart block due to digoxin (unless primarily related to supraventricular tachycardia) and in the setting of massive digitalis overdosage (see Massive Digitalis Overdosage subsection).

Massive Digitalis Overdosage: Manifestations of life-threatening toxicity include ventricular tachycardia or ventricular fibrillation, or progressive bradyarrhythmias, or heart block. The administration of more than 10 mg of digoxin in a previously healthy adult, or more than 4 mg in a previously healthy child, or a steady-state serum concentration greater than 10 ng/mL often results in cardiac arrest.

DIGIBIND should be used to reverse the toxic effects of ingestion of a massive overdose. The decision to administer DIGIBIND to a patient who has ingested a massive dose of digoxin but who has not yet manifested life-threatening toxicity should depend on the likelihood that life-threatening toxicity will occur (see above).

Patients with massive digitalis ingestion should receive large doses of activated charcoal to prevent absorption and bind digoxin in the gut during enteroenteric recirculation. Emesis or gastric lavage may be indicated especially if ingestion has occurred within 30 minutes of the patient's presentation at the hospital. Emesis should not be induced in patients who are obtunded. If a patient presents more than 2 hours after ingestion or already has toxic manifestations, it may be unsafe to induce vomiting or attempt passage of a gastric tube, because such maneuvers may induce an acute vagal episode that can worsen digitalis-related arrhythmias.

Severe digitalis intoxication can cause a massive shift of potassium from inside to outside the cell, leading to life-threatening hyperkalemia. The administration of potassium supplements in the setting of massive intoxication may be hazardous and should be avoided. Hyperkalemia caused by massive digitalis toxicity is best treated with DIGIBIND; initial treatment with glucose and insulin may also be required if hyperkalemia itself is acutely life-threatening.

DOSEAGE AND ADMINISTRATION:

General: Recommended dosages of digoxin may require considerable modification because of individual sensitivity of the patient to the drug, the presence of associated conditions, or the use of concurrent medications.

Parenteral administration of digoxin should be used only when the need for rapid digitalization is urgent or when the drug cannot be taken orally. Intramuscular injection can lead to severe pain at the injection site, thus intravenous administration is preferred. If the drug must be administered by the intramuscular route, it should be injected deep into the muscle followed by massage. No more than 500 mcg (2 mL) should be injected into a single site.

LANOXIN Injection can be administered undiluted or diluted with a 4-fold or greater volume of Sterile Water for Injection, 0.9% Sodium Chloride Injection, or 5% Dextrose Injection. The use of less than a 4-fold volume of diluent could lead to precipitation of the digoxin. Immediate use of the diluted product is recommended.

If tuberculin syringes are used to measure very small doses, one must be aware of the problem of inadvertent overadministration of digoxin. The syringe should not be flushed with the parenteral solution after its contents are expelled into an indwelling vascular catheter.

Slow infusion of LANOXIN Injection is preferable to bolus administration. Rapid infusion of digitalis glycosides has been shown to cause systemic and coronary arteriolar constriction, which may be clinically undesirable.

Caution is thus advised and LANOXIN Injection should probably be administered over a period of 5 minutes or longer. Mixing of LANOXIN Injection with other drugs in the same container or simultaneous administration in the same intravenous line is not recommended.

In selecting a dose of digoxin, the following factors must be considered:

1. The body weight of the patient. Doses should be calculated based upon lean (i.e., ideal) body weight.
2. The patient's renal function, preferably evaluated on the basis of estimated creatinine clearance.
3. The patient's age. Infants and children require different doses of digoxin than adults. Also, advanced age may be indicative of diminished renal function even in patients with normal serum creatinine concentration (i.e., below 1.5 mg/dL).
4. Concomitant disease states, concurrent medications, or other factors likely to alter the pharmacokinetic or pharmacodynamic profile of digoxin (see PRECAUTIONS).

Serum Digoxin Concentrations: In general, the dose of digoxin used should be determined on clinical grounds. However, measurement of serum digoxin concentrations can be helpful to the clinician in determining the adequacy of digoxin therapy and in assigning certain probabilities to the likelihood of digoxin intoxication. About two-thirds of adults considered adequately digitalized (without evidence of toxicity) have serum digoxin concentrations ranging from 0.8 to 2.0 ng/mL. However, digoxin may produce clinical benefits even at serum concentrations below

Corrected Ccr (mL/min per 70 kg)*	kg	50	60	70	80	90	100	Number of Days Before Steady State Achieved†
	lb	110	132	154	176	198	220	
0		75‡	75	100	100	125	150	22
10		75	100	100	125	150	150	19
20		100	100	125	150	150	175	16
30		100	125	150	150	175	200	14
40		100	125	150	175	200	225	13
50		125	150	175	200	225	250	12
60		125	150	175	200	225	250	11
70		150	175	200	225	250	275	10
80		150	175	200	250	275	300	9
90		150	200	225	250	300	325	8
100		175	200	250	275	300	350	7

*Daily maintenance doses have been rounded to the nearest 25-mcg increment.

†Ccr is creatinine clearance, corrected to 70 kg body weight or 1.73 m² body surface area. For adults, if only serum creatinine concentrations (Scr) are available, a Ccr (corrected to 70 kg body weight) may be estimated in men as (140 - Age)/Scr. For women, this result should be multiplied by 0.85. Note: This equation cannot be used for estimating creatinine clearance in infants or children.

‡If no loading dose administered.

§75 mcg = 0.075 mg

Example: Based on the above table, a patient in heart failure with an estimated lean body weight of 70 kg and a Ccr of 60 mL/min should be given a dose of 175 mcg (0.175 mg) daily of LANOXIN Injection. If no loading dose is administered, steady-state serum concentrations in this patient should be anticipated at approximately 11 days.

Infants and Children: See the full prescribing information for LANOXIN Injection Pediatric for specific recommendations.

It cannot be overemphasized that dosage guidelines provided are based upon average patient response and substantial individual variation can be expected. Accordingly, ultimate dosage selection must be based upon clinical assessment of the patient.

Atrial Fibrillation: Peak digoxin body stores larger than the 8 to 12 mcg/kg required for most patients with heart failure and normal sinus rhythm have been used for control of ventricular rate in patients with atrial fibrillation. Doses of digoxin used for the treatment of chronic atrial fibrillation should be titrated to the minimum dose that achieves the desired ventricular rate control without causing undesirable side effects. Data are not available to establish the appropriate resting or exercise target rates that should be achieved.

Dosage Adjustment When Changing Preparations: The difference in bioavailability between LANOXIN Injection, LANOXICAPS and LANOXIN Elixir Pediatric or LANOXIN Tablets must be considered when changing patients from one dosage form to another.

Doses of 100 mcg (0.1 mg) and 200 mcg (0.2 mg) of LANOXICAPS are approximately equivalent to 125-mcg (0.125-mg) and 250-mcg (0.25-mg) doses of LANOXIN Tablets and Elixir Pediatric, respectively (see Table 1 in CLINICAL PHARMACOLOGY: Pharmacokinetics).

HOW SUPPLIED:

LANOXIN (digoxin) Injection, 500 mcg (0.5 mg) in 2 mL (250 mcg [0.25 mg] per mL); Boxes of 10 (NDC 0173-0260-10) and 50 ampuls (NDC 0173-0260-35).

Store at 15° to 25°C (59° to 77°F) and protect from light.

GlaxoWellcome

Manufactured by
Catalytic Pharmaceuticals, Inc.
Greenville, NC 27834
for Glaxo Wellcome Inc.
Research Triangle Park, NC 27709

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May 1998



RL-563

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 9330/S020

CHEMISTRY REVIEW(S)


JUN 1 - 1998

CHEMIST'S REVIEW		1. ORGANIZATION HFD-110	2. NDA Number 09-330
3. Name and Address of Applicant (City & State) Glaxo Wellcome Inc. Five Moore Drive PO Box 13398 Research Triangle Park, NC 27709			4. Supplement(s) Number(s) Date(s) SLR-020 5/12/98
5. Drug Name Lanoxin	6. Nonproprietary Name Digoxin		8. Amendments & Other (reports, etc) - Dates
7. Supplement Provides For: Revised labeling.			
9. Pharmacological Category Cardiotonic glycoside	10. How Dispensed <input checked="" type="checkbox"/> Rx <input type="checkbox"/> OTC		11. Related IND(s)/NDA(s)/DMF(s)
12. Dosage Form(s) Injection	13. Potency(ies) 0.25 mg/mL 0.1 mg/mL (pediatric)		
14. Chemical Name and Structure			15. Records/Reports Current <input type="checkbox"/> Yes <input type="checkbox"/> No Reviewed <input type="checkbox"/> Yes <input type="checkbox"/> No
16. Comments: SPECIAL SUPPLEMENT - CHANGES BEING EFFECTED DESCRIPTION section is satisfactory for both Lanoxin (digoxin) Injection and Lanoxin (digoxin) Injection Pediatric. For HOW SUPPLIED storage statement, we recommend the following: <div style="text-align: center;">  </div>			
17. Conclusions and Recommendations: Satisfactory for DESCRIPTION. HOW SUPPLIED section - see above statement.			
18. REVIEWER			
Name Danute G. Cunningham	Signature 		Date Completed May 22, 1998
Distribution: <input checked="" type="checkbox"/> Original Jacket <input type="checkbox"/> Reviewer <input type="checkbox"/> Division File <input type="checkbox"/> CSO <input type="checkbox"/> District			

09330S20.SUP

5-29-98

JUN 26 1998

CHEMIST'S REVIEW		1. ORGANIZATION HFD-110		2. NDA Number 09-330	
3. Name and Address of Applicant (City & State) Glaxo Wellcome Inc. Five Moore Drive PO Box 13398 Research Triangle Park, NC 27709				4. Supplement(s) Number(s) Date(s) SLR-020 6/9/98 (AF)	
5. Drug Name Lanoxin		6. Nonproprietary Name Digoxin		8. Amendments & Other (reports, etc) - Dates	
7. Supplement Provides For: Labeling.					
9. Pharmacological Category Cardiotonic glycoside		10. How Dispensed <input checked="" type="checkbox"/> Rx <input type="checkbox"/> OTC		11. Related IND(s)/NDA(s)/DMF(s)	
12. Dosage Form(s) Injection		13. Potency(ies) 0.25 mg/mL 0.1 mg/mL (pediatric)			
14. Chemical Name and Structure				15. Records/Reports Current <input type="checkbox"/> Yes <input type="checkbox"/> No Reviewed <input type="checkbox"/> Yes <input type="checkbox"/> No	
16. Comments: DESCRIPTION section - satisfactory. HOW SUPPLIED section - satisfactory.					
17. Conclusions and Recommendations: DESCRIPTION and HOW SUPPLIED sections - satisfactory.					
18. REVIEWER					
Name Danute G. Cunningham		Signature 		Date Completed June 19, 1998	
Distribution: <input checked="" type="checkbox"/> Original Jacket <input type="checkbox"/> Reviewer <input type="checkbox"/> Division File <input type="checkbox"/> CSO					

09330S20.AM1

6-26-98

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 9330/S020

ADMINISTRATIVE DOCUMENTS

JUL 15 1998

RHPM REVIEW OF LABELING

NDA 9-330/S-020 Lanoxin (digoxin) Injection and Pediatric Injection
18-118/S-016 Lanoxicaps (digoxin in solution) Capsules

Sponsor: Glaxo Wellcome Inc.
Five Moore Drive
Research Triangle Park, NC 27709

Date of Submission: May 12, 1998 (both)

Date of FPL Submissions: June 9, 1998 (both)

BACKGROUND

These supplemental applications were submitted to provide consistency with the labeling recently approved for NDA 20-405 (Lanoxin Tablets). The text of the labeling parallels the text of the revised labeling approved for the Lanoxin tablet NDA except for the product-specific differences. The supplemental applications were submitted as changes being effected, but final printed labeling was not included with the initial submission. Regulations state (21 CFR 314.101(a)) that the required number of copies of final printed labeling must accompany the initial submission for a changes being effected supplement. The firm was informed that the submissions could not be taken as changes being effected supplements without FPL. The firm submitted the required FPL on June 9, 1998.

REVIEW

The labeling was reviewed and found to be comparable to the approved labeling for NDA 20-405. Product-specific differences were present, but all were appropriate and present in previous labeling.

Upon review the following error in the original draft was discovered:

Under **CLINICAL PHARMACOLOGY, Chronic Heart Failure**, third paragraph, first line the phrase "time..." should have said "...with a trend to increase

The firm will be asked to make this correction in the supplemental applications as well as in the labeling for NDA 20-405.

In addition, the review chemist requested that the following change in the storage statement under **HOW SUPPLIED** be recommended:

An acknowledgement and approval letter will be drafted for Dr. Lipicky's signature. The letter will request that the above change in the **CLINICAL PHARMACOLOGY, Chronic Heart Failure** section be made at next printing and also recommend that the change in storage conditions be considered. A supplemental application would not be required for either of the above changes. They should, however, be reported in the next annual report.

Gary Buehler
Project Manager

7/15/98

Orig NDAs
HFD-110
HFD-110 GBuehler, HFD-110 SBenton, HF-2 MEDWATCH